Abstract: 9509

Initial efficacy and safety of RP1 + nivolumab in patients with anti–PD1–failed melanoma from the ongoing phase 1/2 IGNYTE study

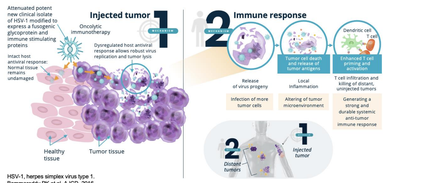
Bartosz Chmielowski[1], Mohammed M. Milhem[2], Joseph J. Sacco[3], Tawnya Lynn Bowles[4], Katy K. Tsai[5], Gino K. In[6], Eva Muñoz-Couselo[7], Ari M. VanderWalde[8], Jason Alan Chesney[9], Judith Michels[10], Adel Samson[11], Georgia M. Beasley[12], Dirk Schadendorf[13], Fade Mahmoud[14], Michael K. Wong[15], Trisha M. Wise-Draper[16], Junhong Zhu[17], Praveen K. Bommareddy[17], Jeannie W. Hou[17], Mark R. Middleton[18]

[1]Jonsson Comprehensive Cancer Center, University of California Los Angeles, Los Angeles, CA, USA; [2]Holden Comprehensive Cancer Center, University of Iowa, Iowa City, IA, USA; [3]Clatterbridge Cancer Center, Wirral, UK and University of Liverpool, Liverpool, UK; [4]Intermountain Medical Center, Murray, UT, USA; [5]Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, CA, USA; [6]University of Southern California Norris Comprehensive Cancer Center, Los Angeles, CA, USA; [7]Vall d'Hebron Institute of Oncology (VHIO) and Vall d'Hebron Hospital Medical Oncology Department, Barcelona, Spain; [8]West Cancer Center and Research Institute, Germantown, TN, USA; [9]James Graham Brown Cancer Center, University of Louisville, Louisville, KY, USA; [10]Gustave Roussy, Département de Médecine Oncologique, Villejuif, France; [11]Leeds Institute of Medical Research at St. James, University of Leeds, Leeds, UK; [12]Duke Cancer Institute, Duke University, Durham, NC, USA; [13]West German Cancer Center, University Hospital Essen, Essen, Germany; [14]The T.W. Lewis Melanoma Center of Excellence, Banner MD Anderson Cancer Center at Banner Gateway Medical Center, Gilbert, AZ, USA; [15]University of Texas MD Anderson Cancer Center, Houston, TX, USA; [16]University of Cincinnati, Cincinnati, OH, USA; [17]Replimune Inc., Woburn, MA, USA; [18]Churchill Hospital and the University of Oxford, Oxford, UK

Background

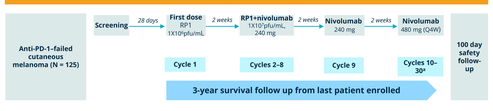
- Patients with melanoma who progress on anti–PD-1 therapy (anti–PD1–failed) have limited treatment options[1]
- Tumor-directed oncolytic immunotherapy (TDOI) may provide a treatment option for such patients
- RP1 (vusolimogene oderparepvec) is an HSV-1–based TDOI expressing human GM-CSF and a fusogenic protein (GALV-GP-R−)[2]
- Previously, RP1+nivolumab was tested in 30 melanoma patients, including 16 cutaneous melanoma patients who had previously received anti-PD1 +/- anti-CTLA-4 where a 37.5% ORR was seen
- Subsequently a registration-directed 125 patient cohort of anti-PD1 failed cutaneous melanoma patients was opened based on that data
- Here, we present initial data from the first 75 patients from the registration-directed anti–PD1–failed melanoma cohort, and also those patients combined with the 16 anti-PD1 failed patients from the prior melanoma cohort (n=91 in total), both from the ongoing phase 1/2 IGNYTE clinical trial (NCT03767348)

Tumor-directed oncolytic immunotherapy (TDOI) mechanism of action



HSV-1, herpes simplex virus type 1.
Bommareddy PK et al. *JLCD*. 2016

Study Design



Primary objectives
- To assess the safety and tolerability of RP1 in combination with nivolumab
- To assess the efficacy of RP1 in combination with nivolumab as determined by ORR using modified RECIST 1.1 criteria (PD must be confirmed; biopsy can be used to confirm CR)

Secondary objectives
To assess the efficacy of RP1 in combination with nivolumab as determined by DOR, CR rate, DCR, PFS, and 1- and 2-year OS

Key eligibility
Advanced or metastatic anti-PD1 failed cutaneous melanoma; at least 1 measurable and injectable lesion (≥ 1cm LD); adequate organ function; no prior treatment with oncolytic therapy; ECOG PS 0-1

Criteria for Anti-PD1-failed:
At least 8 weeks of prior anti-PD-1, confirmed progression while on anti–PD-1; anti-PD-1 must be the last therapy before the clinical trial. Patients on prior adjuvant therapy must have progressed while on prior adjuvant treatment (confirmed by biopsy)

Note: Dosing with nivolumab begins at dose 2 of RP1 (C2D15). *Option to reinitiate RP1 for 8 cycles if criteria are met. C, cycle; CR, complete response; D, day; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; LD, longest diameter; OS, overall survival; PFS, progression-free survival. Median follow up for this data snapshot is 75.9 weeks. As a data snapshot from an ongoing study, the current data is subject to potential non-material future changes as the study database continues to evolve; however, all attempts have been made to ensure that the data presented is as clean as possible.

Results: Patient demographics

	Initial IGNYTE melanoma cohort anti–PD-1–failed patients (n=16)	Anti–PD-1–failed melanoma cohort (n= 75)	Combined (n=91)
Age			
Median (range)	60 (28–78)	60 (31–91)	60 (28–91)
Sex, n (%)			
Female	7 (43.8)	22 (29.3)	29 (31.9)
Male	9 (56.3)	53 (70.7)	62 (68.1)
Disease stage, n (%)			
IIIb	0 (0.0)	2 (2.7)	2 (2.2)
IIIc	0 (0.0)	27 (36.0)	27 (29.7)
IVM1a	3 (18.8)	13 (17.3)	16 (17.6)
IVM1b	6 (37.5)	13 (17.3)	19 (20.9)
IVM1c	7 (43.8)	20 (26.7)	27 (29.7)
BRAF status			
Wild-type	16 (100.0)	48 (64.0)	64 (70.3)
Mutant	0 (0.0)	27 (36.0)	27 (29.7)
Prior therapy (all patients had prior anti-PD1), n (%)			
Prior anti–PD-1 but not also anti–CTLA-4	7 (43.8)	52 (69.3)	59 (64.8)
Also prior anti–CTLA-4	9 (56.3)	23 (30.7)	32 (35.2)
Also prior BRAF/MEK inhibition	0 (0.0)	8 (10.7)	8 (8.8)
Also prior other therapy	2 (12.5)	7 (9.3)	9 (9.9)
Received prior anti–PD-1 only as adjuvant therapy	3 (18.8)	29 (38.7)	32 (35.2)
Anti-PD1 resistance type, n (%)			
Primary	9 (56.3)	41 (54.7)	50 (54.9)
Secondary	6 (37.5)	32 (42.7)	38 (41.8)
Unknown	1 (6.2)	2 (2.7)	3 (3.3)
PD-L1 status			
Positive (PD-L1 ≥1%)	5 (31.3)	21 (28.0)	26 (28.6)
Negative (PD-L1 <1%)	7 (43.7)	44 (58.7)	51 (56.0)
Unknown	4 (25.0)	10 (13.3)	14 (15.4)
LDH, n (%)			
LDH ≤ULN	13 (81.2)	51 (68.0)	64 (70.3)
LDH >ULN	3 (18.8)	23 (30.7)	26 (28.6)
Unknown	0 (0.0)	1 (1.3)	1 (1.1)
Baseline ECOG PS status, n (%)			
0	13 (81.2)	48 (64.0)	61 (67.0)
1	3 (18.8)	27 (36.0)	30 (33.0)

BRAF, rapidly accelerated fibrosarcoma B-type; CTLA-4, cytotoxic T-lymphocyte associated protein 4; ECOG PS, Eastern Cooperative Oncology Group performance status; LDH, lactate dehydrogenase; MEK, mitogen-activated extracellular signal-regulated kinase; PD-1, programmed cell death protein 1; ULN, upper limit of normal. Primary resistance = best response of PD, or SD for <6 months on the prior course of anti-PD1[1]; for prior adjuvant patients, progressed within 6 months of starting anti-PD1; secondary resistance = Best response of PR, CR, or SD >6months on the prior course of anti-PD1[1]; for adjuvant patients, progressed after 6 months of starting anti-PD1.

- Most patients (54.9%) had primary resistance to anti-PD1 therapy, ie did not respond to or or progressed within 6 months on their prior course of anti-PD1 (including while on adjuvant anti-PD1 therapy) -- with confirmation of progression while on continued anti-PD1 therapy being required to be eligible for the IGNYTE clinical trial

Results: Efficacy & Safety

Objective response rates

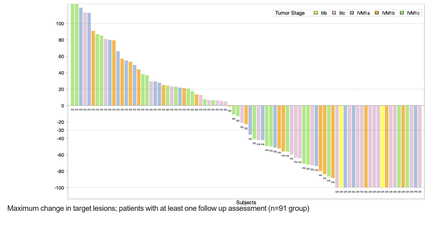
- The overall objective response rate (ORR) was 37.4%; ORR of at least 28.3% in all subgroups analyzed, including in patients:
  - Having failed anti-CTLA-4 therapy as well as anti-PD1 therapy (34.4% ORR)
  - With Stage IVM1b/c disease (28.3% ORR)
  - Who progressed *while on* prior adjuvant anti-PD1 therapy (50% ORR)
    - Patients who progressed *after discontinuing* adjuvant therapy were not eligible for the trial
  - With both primary resistant (36.0% ORR) and secondary resistant (42.1% ORR) disease
- Data from the 75-patient snapshot are consistent with the 16 patients enrolled into the prior melanoma cohort

	N=16	N=75	N=91						
n (%)	Prior patients (n=16)	Data snapshot patients (n=75)	All patients (n=91)	Prior adjuvant anti–PD-1 only (n=32)	Prior anti–PD-1 other than adjuvant (n=59)	Prior anti–PD-1 & anti–CTLA-4 (n=32)	Stage IIIb/IIIc/IVa (n=45)	Stage IVb/IVc (n=46)	Primary resistance to anti-PD1 (n=50)**	Secondary resistance to anti-PD1 (n=38)**
Best overall response										
CR	2 (12.5)	15 (20.0)	17 (18.7)	9 (28.1)	8 (13.6)	3 (9.4)	13 (28.9)	4 (8.7)	12 (24.0)	5 (13.2)
PR	4 (25.0)	13 (17.3)*	17 (18.7)	7 (21.9)	10 (16.9)	8 (25.0)	8 (17.8)	9 (19.6)	6 (12.0)	11 (28.9)
SD	1 (6.3)	13 (17.3)	14 (15.4)	6 (18.8)	8 (13.6)	5 (15.6)	5 (11.1)	9 (19.6)	7 (14.0)	7 (18.4)
PD	8 (50.0)	31 (41.3)	39 (42.9)	10 (31.3)	29 (49.2)	13 (40.6)	19 (42.2)	20 (43.5)	24 (48.0)	12 (31.6)
ORR	**37.5%**	**37.3%**	**37.4%**	**50.0%**	**30.5%**	**34.4%**	**46.7%**	**28.3%**	**36.0%**	**42.1%**

CTLA-4, cytotoxic T-lymphocyte associated protein 4; CR, complete response; DCR, disease control rate; ORR, objective response rate; PD-1, programmed cell death protein 1; PD, progressive disease; PR, partial response; SD, stable disease. Investigator assessed responses, the primary analysis for the 125-patient cohort will be by central review. *One PR not confirmed, **Resistance type is unknown for 3 patients. Response data presented is by investigator assessment; the primary analysis from the study will be by blinded, independent central review.

Depth of response

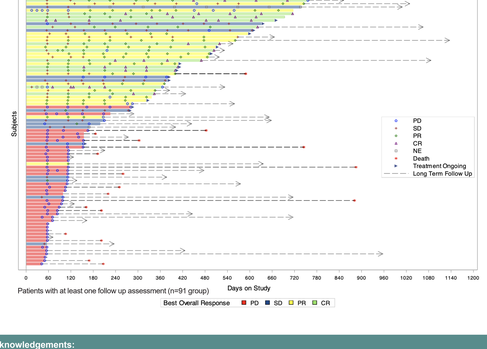
- Frequent and deep responses were seen, with >50% of patients having target (RECIST) tumor reduction
- Responses were seen irrespective of stage of disease, including CRs in patients with stage IV M1b/c disease



Maximum change in target lesions; patients with at least one follow up assessment (n=91 group)

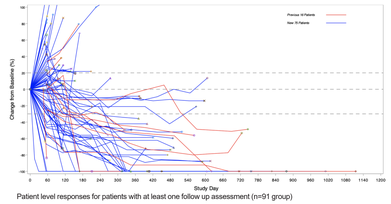
Duration of response

- Responses are generally durable, and often deepen over time, indicating systemic overall benefit
- 85% of responses are ongoing, with 71% of responders out over 1 year from starting therapy



Kinetics of response

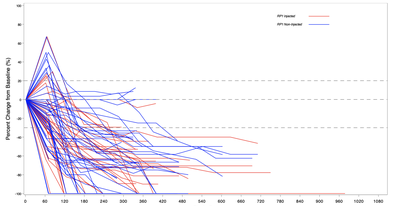
- Responses are durable, and tend to deepen over time



Patient level responses for patients with at least one follow up assessment (n=91 group)

Response kinetics for injected & uninjected lesions

- Systemic effects across the entire disease burden are seen (please see the images for all responding patients through the link provided to the right), showing response of:
  - Visceral lesions following both deep and superficial injection
  - Bulky lesions
  - Up to >20cm of total tumor burden and up to >10cm of uninjected disease
- 70.4% of responding patients had lesions which were not injected, including patients where only a small minority of lesions were injected
- The response of individual injected and uninjected lesions for responding patients is shown below
  - Injected (red lines) and uninjected (blue lines) lesions respond with similar kinetics, including for durability of response
  - Depth of lesion response was independent of whether the lesion was injected
  - The figure demonstrates the large number of uninjected lesions which responded (blue lines)



Change in size of individual injected and uninjected lesions (including both target and non-target lesions for RECIST assessment), as measured from CT/MRI scans for radiologically assessable lesions (n=75 group). *58/75 patients had lesions which were not injected, of which 15 achieved a response on the basis of uninjected lesions only (ORR of 25.9% on the basis of uninjected lesions only).

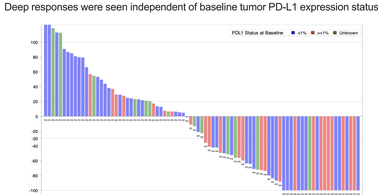
Influence of baseline tumor PD-L1 & BRAF mutation status

- The majority of patients were PD-L1 negative, with responses being seen irrespective of PD-L1 status
- Most patients were BRAF wild-type, as might be expected as the last prior line of therapy was required to have been anti-PD1, on which confirmed progression was required to have been seen
  - BRAF wild-type and BRAF mutant patients were similarly responsive

PD-L1/BRAF Status	All Patients (N=91) (n/%)	ORR (n/%)
PD-L1 <1%, n (%)	51 (56.0)	17 (33.3)
PD-L1 ≥1%, n (%)	26 (28.6)	15 (57.6)
PD-L1 Unknown, n (%)	14 (15.4)	2 (14.3)
BRAF wild-type	64 (70.3)	25 (39.1)
BRAF mutant	27 (29.7)	9 (33.3)

Depth of response by baseline tumor PD-L1 expression status

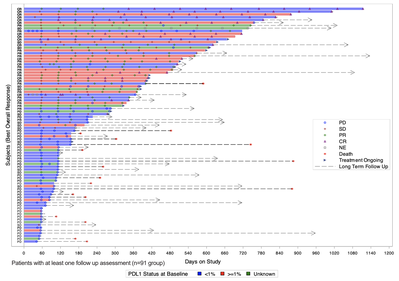
- Deep responses were seen independent of baseline tumor PD-L1 expression status



Maximum change in target lesions; patients with at least one follow up assessment (n=91 group)

Duration of response by baseline tumor PD-L1 status

- Durable responses are observed in both PD-L1 negative as well as PD-L1 positive patients

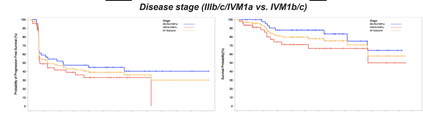


Progression-free & overall survival

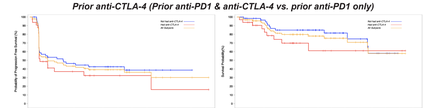
- Both progression-free survival (PFS) and overall survival (OS) appear promising for the population enrolled (yellow lines)
- This includes when broken down by disease stage (Stage IIIb/c/IVM1a vs IVM1b/c), prior therapy (progressed on prior anti-PD1 or on prior anti-PD1 and anti-CTLA-4), prior treatment setting (prior adjuvant anti-PD1 only vs anti-PD1 other than adjuvant therapy), whether the patient responded or not to RP1+nivolumab, and whether all lesions were injected with RP1 or not (red and blue lines)
  - By far the greatest impact on PFS & OS was whether or not the patient responded to RP1 combined with nivolumab
  - There was no impact of whether or not all lesions were injected with RP1

PFS* **OS**

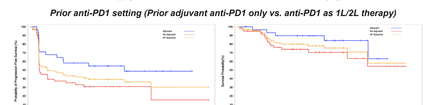
Disease stage (IIIb/c/IVM1a vs. IVM1b/c)



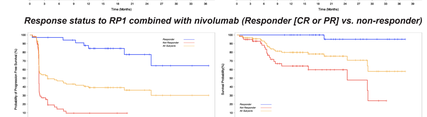
Prior anti-CTLA-4 (Prior anti-PD1 & anti-CTLA-4 vs. prior anti-PD1 only)



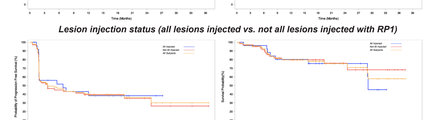
Prior anti-PD1 setting (Prior adjuvant anti-PD1 only vs. anti-PD1 as 1L/2L therapy)



Response status to RP1 combined with nivolumab (Responder [CR or PR] vs. non-responder)



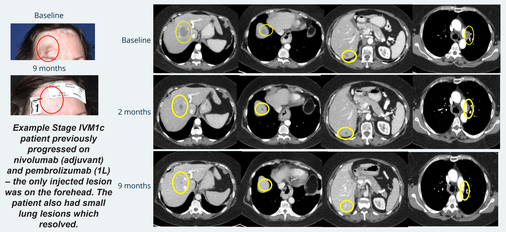
Lesion injection status (all lesions injected vs. not all lesions injected with RP1)



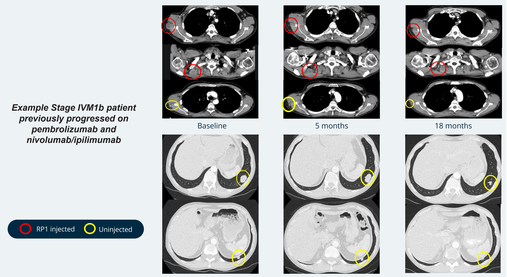
*The protocol requires PD to be confirmed, to allow for pseudoprogression. The definition of a PFS event is therefore PD where PD was subsequently confirmed or no further assessment was done (date of event = date of initial PD), any event of PD where treatment was then discontinued, or death from any cause. PD, progressive disease; PFS, progression-free survival; OS, overall survival. Data for n=91 group.

Systemic responses in patients with visceral disease, moderate-high tumor burden, and bulky disease – *scans for all responding patients can be found at* Patient-Images-Appendix

Visceral disease following superficial RP1 injection

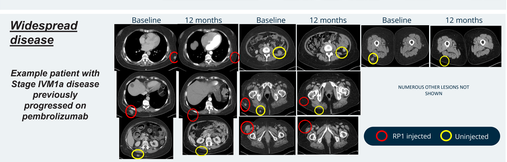


Example Stage IVM1c patient previously progressed on nivolumab (adjuvant) and pembrolizumab (1L) – the only injected lesion was on the forehead. The patient also had small lung lesions which resolved.



Example Stage IVM1b patient previously progressed on pembrolizumab and nivolumab/ipilimumab

Widespread disease



Example patient with Stage IVM1a disease previously progressed on pembrolizumab

Treatment-related adverse events for patients treated with RP1 combined with nivolumab (n=91)

- Most treatment-related adverse events were grade 1 or 2 and were indicative of systemic immune activation, combined with the underlying safety profile of nivolumab

Preferred term, n (%)	Grade 1–2 (>10%)	Grade 3	Grade 4	Grade 5	Total (n=91)
Chills	34 (37.4)	0	0	0	34 (37.4)
Fatigue	31 (34.1)	2 (2.2)	0	0	32 (35.2)
Pyrexia	26 (28.6)	0	0	0	26 (28.6)
Nausea	24 (26.4)	0	0	0	24 (26.4)
Influenza like illness	12 (13.2)	0	0	0	12 (13.2)
Diarrhoea	10 (11.0)	1 (1.1)	0	0	10 (11.0)

Grade 3 events were one each of maculopapular rash, immune-mediated hepatitis, enterocolitis, immune-mediated enterocolitis, edema, paresthesia, memory impairment, aseptic meningitis, infusion-related reaction, abdominal pain, MALT lymphoma, increased amylase, increase LFT, arthritis, arthralgia, palmar-plantar erythrodysesthesia, muscular weakness and rash. One Grade 4 event each of lipase increased and cytokine release syndrome. There was no treatment-related Grade 5 event.

Conclusions

- RP1 combined with nivolumab continues to have an attractive safety profile
- Clinically meaningful durable activity is seen across the range of anti-PD1 failed settings enrolled
  - 37.4% ORR, including 28.3% in Stage IVM1b/c patients and 34.4% in patients who have progressed on both anti-PD1 and anti-CTLA-4
  - Responses are durable (85% of responses have been maintained to date)
  - Responses are frequently seen in uninjected as well as injected lesions, including in patients with moderate-high tumor burden and with visceral disease
  - Responses are seen irrespective of PDL1 or BRAF status
  - PFS & OS are promising, including when broken down by prognostic factors, and injection/ response status

The IGNYTE study is currently recruiting patients. To learn more about enrolling your patient, contact clinicaltrials@replimune.com

Additional information can be obtained by visiting Clinicaltrials.gov (NCT03767348).

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2. Thomas S, et al. *J Immunother Cancer*. 2019;7(1):214.
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Study sponsor:

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